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TITLE: Brain Mechanisms of Affective Language Comprehension in Autism Spectrum Disorders

PRINCIPAL INVESTIGATOR: Dr. Donald Joseph Bolger

CONTRACTING ORGANIZATION: University of Maryland College Park, MD 20742

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17. LIMITATION

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18. NUMBER

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19a. NAME OF RESPONSIBLE PERSON

19b. TELEPHONE NUMBER (include area

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code)

16. SECURITY CLASSIFICATION OF:

b. ABSTRACT

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a. REPORT

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1. INTRODUCTION:

The project, Brain Mechanisms of Affective Language Comprehension in Autism Spectrum Disorders, is an investigation into the behavioral and biological bases of the social communication deficits in individual with autism spectrum disorders (ASD). Autism is characterized by impairments in both social interaction and language. While these domains are often studied separately, their interaction presents the greatest challenge to individuals with ASD. Effective social interactions depend on fluent and flexible language comprehension. An area of particular difficulty in ASD may be in the ability to comprehend the social or emotional content of the speaker's message. The primary goals of this project are to a) identify whether this comprehension deficit stems from failures in processing affect and meaning from individual emotion words or from a general difficulty in processing meaning from words with abstract referents; and b) whether the source of this deficit emerges from difficulties inferring emotional states from, largely social, contexts. Neuroimaging measures provide an objective measure of affective processing and provide insight into brain mechanisms underlying impaired affective comprehension. Functional MRI is currently being collected from typically developing young adults (18-24) and those with high-functioning autism during multiple experiments. In the study described in the proposal, social scenarios describing emotionally evocative situations will be presented auditorally in vignettes and then participants will be asked to respond about the protagonist's feelings with a congruent or incongruent emotional word: "He/She felt sad/happy."

2. KEYWORDS:

Affective Language, High functioning autism spectrum disorder, functional Magnetic Resonance Imaging (fMRI), Social-emotional processes, emotional inference task

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims 1a & 1b: Determine whether individuals with autism spectrum disorder fail to draw emotional inferences from linguistic contexts and whether these putative deficits are shown with respect to activation elicited in emotion processing regions of the brain.		Completed	Accomplishments	
Major Task 1: Experimental Design	Months			
Subtask 1: Finalize the design for the research protocols and analysis to be performed in all years. This includes the development of protocols and behavioral and neural assessments. This task also includes any changes in design of fMRI tasks and scanning protocols as necessary. The design will remain constant throughout the duration of the project. Participating teams:	1-3	9/10/2015	Finalized scan parameters and tested experimental protocols in mock sessions.	
Subtask 2: Submit documents for local IRB* review The teams will prepare and submit any revised protocol materials for human participants to the institutional review board (IRB) of the University of Maryland. The team will work with the IRB to expedite the review process and address any human subjects concerns.	1	10/21/2015	HRPO required changes to protocol approved by UMD IRB.	
Subtask 3: Submit IRB approval and necessary documents for HRPO* review.	2-3	10/21/2015	HRPO approval: 11/4/2014 documented: 12/5/2014	
Milestone #1: HRPO** approval received	2-3			
Major Task 2: Human Subject Experimentation.				
 Subtask 3: Recruitment of Participants. The team will create a recruitment protocol particularly for individuals with Autism Spectrum Disorder. The team will utilize database information from the Interactive Autism Network (IAN) as well as outreach to local organizations that support individuals and families with ASD. 	3-6			

 Subtask 4: Running of Participants Participants will be recruited during the first year and processed per the approved protocol, including behavioral assessments and neuroimaging protocols. Participants with ASD will be targeted in the early portion of the study. Age and gender matched controls will be targeted in the latter half of the study. 	6-30	As of 9/15/2016 ~50% of target goal	15 participants in ASD group and 16 in Typical group completed
 Subtask 5: Initial Analysis of behavioral and imaging data Conduct analysis within groups to determine the neural response in TD individuals making emotional inferences from language context and whether individuals with ASD fail to so. 	30	As of 9/15/2016	Dissertation Completed by Dr. Lesley Sand (9/11/2015) Presentation of Preliminary Results at IMFAR (5/12/2016)
Milestone #2: Co-author manuscript on the underlying neural system in Typically developing individuals when making emotional inferences.	30-32	10/4/2015	Manuscript currently under revision
 Subtask 6: Full analysis of functional MRI data during EIT task Conduct within subjects and group differences to determine whether individuals with ASD have aberrant neural activity relative to typical controls when making emotional inferences. 	30		
Milestone #3: Co-author manuscript on group differences in fMRI activation between groups on the EIT task	32-36		
Specific Aims 2: Determine whether functional connectivity between emotion and language regions is reduced in individuals with ASD during the EIT task and at rest.	Timeline 30-36		
Major Task 3: Data analysis of functional connectivity data in fMRI.			
Subtask 7: Analysis of functional connectivity data during EIT task and resting state stages of fMRI.	30		
Milestone #4: Co-author manuscript on group differences in functional connectivity between groups on the EIT task and rsfMRI.	32-36		

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

There were two major activities in the second year of the project: 1) the recruitment and running of participants through the approved protocol, and 2) the reporting of results in the form of a manuscript (Milestone 2, submitted in October, 2015, currently under revision for resubmission) and in the presentation of preliminary results.

Our primary goal this reporting period was the continued recruitment and running of participants through the protocol. Whereas we were quite successful in our initial recruitment efforts in Year 1, whence we had run 31 participants (15 ASD and 16 typical controls), however, this past year proved much more difficult to recruit individuals with ASD. Participants were recruited from a number of sources including online listservs and bulletin boards as well as local schools specializing in ASD. Recruitment was quiet throughout the year and potential participants did not qualify for the study under the given protocols. Most of these participants with ASD either failed to meet the threshold for language ability or general intelligence, and others were brought in for behavioral assessment but were too anxious to participate in the MRI portion of the experiment. We recruited roughly 14 participants, but none were run successfully through the protocol. In response to our low success rate with subjects meeting the criterion for our study, we enhanced our presence on social media and printed flyers around the region. This has led to an increase in interest based on email traffic, however, many still fail to qualify. As of September, we have gone back to using the IAN network to send out another recruitment blast through their list of contacts. This is what allowed successful recruitment in Year 1.

The other major achievements in the period with respect to deliverables are that the data were preliminarily analyzed as we initially proposed to do in month 30 (Year 3). A brief description of the methods is detailed below. This preliminary analysis was conducted as part of the doctoral dissertation of Dr. Lesley Sand on September 11, 2015 reported during the previous period. During this period, we continued to analyze the data and reported our preliminary findings in two panel discussions at the International Meeting For Autism Research (IMFAR), which is the largest and most well-respected venue for dissemination of research on ASD on May 11-13, 2016 in Baltimore, MD. These findings were also presented by Dr. Bolger in a series of invited to Temple University (March 9) and Penn State University (March 30).

A second major achievement was that Milestone #2, a written manuscript of the effects of the experimental paradigm within neurological typical adults, was also completed and submitted for

publication in October of 2015. The manuscript is currently under revision and will be resubmitted in early November. This milestone was initially scheduled to occur in month 30-32 (Year 3).

Brief Overview

Autism Spectrum Disorders (ASD) are pervasive neurodevelopmental disorders characterized by difficulties in social interaction. One critical aspect of fluent social interactions is the ability to comprehend others' emotional states through language context. ASD individuals have difficulty attributing emotional labels to pictures or sentences as well as reduced memory for emotional words as compared to typically developing peers. As depicted in Figure 1, the current investigation aims to identify the brain mechanisms underlying difficulties with emotional language processing in ASD.

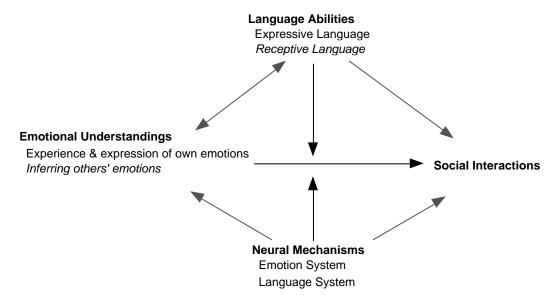


Figure. 1. Summary of mechanisms related to social interactions. The main focus of this research is the ability of individuals with ASD to infer others' emotions; this implies receptive language skills. However, emotional understandings include both one's own physical feelings and expressions of emotion as well as the ability to extend these understandings to others', and language skills include both expressive and receptive capacities. Neural systems related to both language- and emotion processes are well-defined, and impaired in autism.

Our hypothesis is that, unlike TD individuals, individuals with ASD, will not recruit emotion-related brain regions (e.g., the amygdala) while listening to stories with emotional content, suggesting a failure to elicit an appropriate emotional response to stories inferring others emotions. In the first year, we have collected functional and structural magnetic resonance imaging (MRI) data from 31 adolescents and young adults (16-30 years): 16 of whom are typically developing (TD) and 15 with ASD. Participants listened to stories in a task described below that required an emotional or neutral inference followed by a statement (e.g., "She felt [emotion]") for which they will be asked to make a congruity judgment based on the previous

verbal context. Additionally, we predicted that ASD individuals will be less accurate in making congruity judgments about the emotion words (as compared to neutral words) and show reduced activation in regions involved in error monitoring during the presentation of emotion words that are incongruous to the sentence context. These findings would suggest that ASD individuals do not automatically associate a verbal label (e.g., 'panic') with context (e.g., sentence describing panic). Our second goal is to examine whether reduced task-based and resting functional connectivity between emotion and language-related brain regions contributes to these deficits in making emotional inferences from language context. Findings from the current investigation will provide a greater understanding of the neural and cognitive mechanisms underlying difficulties with affective language processing in ASD individuals. Difficulties with understanding others' emotions through language negatively impact the formation and maintenance of close personal relationships in individuals with ASD. Findings from the current proposal can inform the development of more targeted interventions of emotional language comprehension to improve overall quality of life in individuals with ASD.

Methodology

We have developed an emotional inferences task (EIT) that enables us to use event-related fMRI to examine the cortical response to emotionally provocative situations presented verbally (short 12 second stories) and probes whether the participant recognizes the emotion that would be expected ("He/She felt..."). Validation of the EIT was done with 23 healthy adult participants revealing that stories with positive and negative emotional content engaged language and emotion centers of cortex relative to neutral stories matched on complexity. The EIT is well-suited for examining whether and how emotions are inferred from language using cortical measures.

Table 1			
Passage	Valence	Congruent	Incongruent
		Target	Target
The woman could not get over the idea that her ex-boyfriend did not	negative	She felt sad.	She felt
want to be with her anymore. Hearing that he was dating someone new			happy.
made the situation even worse.			
The young man had waited so long for his favorite band to come to	positive	He felt	He felt
town that he could hardly sleep the night before the concert. He		excited.	disgust.
planned to arrive early to get autographs.			
After the race, the jockey was covered head to toe, and he couldn't see	neutral	He felt dirty.	He felt clean.
through his goggles. Days of rain had saturated the track, so the horses			
kicked up great clods as they ran.			

Results

Neurotypical Adults

Our first objective was to ensure the effectiveness of our paradigm on neurotypical adults based on data collected prior to the funding period. Pilot data was provided in the proposal for funding and additional data was collected and analyzed prior to funding to enable us to complete

Milestone #2. As shown in Figure 2, healthy adults show greater activation for emotionally valent stories (Panel B in red) in characteristic brain regions of social-emotional processing (See Appendix B for full results).

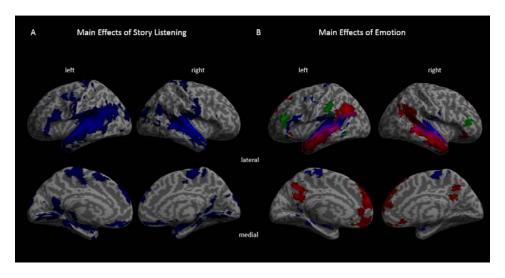


Figure 2. Activation maps illustrating the presence of significant functional activity associated with listening to stories. A) We show t-values for regions showing signal increases for the average effect of stories (positive + negative + neutral) vs. baseline contrast. B) We show t-values for signal increases associated with effect of emotion (positive + negative) vs. neutral in red, neutral vs. emotion in green, and neutral vs. baseline in blue. Regional variations in task-related activity are displayed using a threshold of p < .001 corrected with cluster extent FWE threshold (p<0.05) for t-statistic maps.

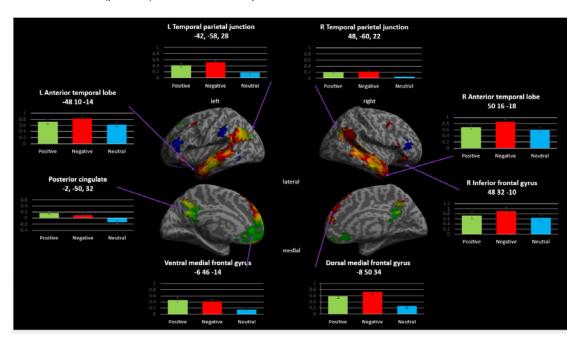


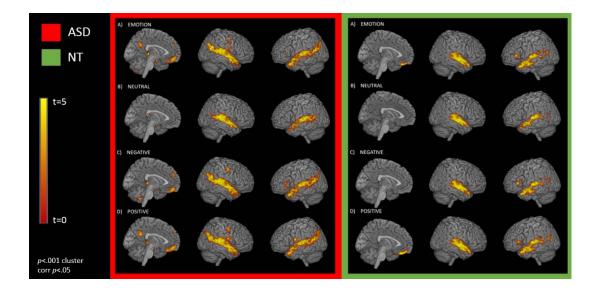
Figure 3. Activation maps illustrating the presence of significant functional activity associated with valence; effect of positive vs. neutral is shown in green, negative vs. neutral is shown in red, and neutral vs. emotion (positive + negative) is shown in blue. Yellow indicates areas of overlap. Regional variations in task-related activity are displayed using a threshold of p < .001 cluster corrected for t-statistic maps. Error bars show standard error.

The data were also analyzed to determine whether these effects were driven by positive or negative valent emotional inferences. Figure 3 displays the activation values in these regions as a function of the positive, negative or neutral valence of the stories that participants heard. Generally, greater activation to negative stories was found on the lateral surface of the brain.

Autism Spectrum Disorder

Having collected roughly half of the data for the current investigation, we conducted preliminary analyses as detailed as Subtask #5 for Human Experimentation. The doctoral thesis for Dr. Sand was submitted in our previous report.

The activation profile for emotionally valent stories in individuals with ASD looks remarkably similar to that of neurotypical adults as shown in Figure 4 below. The activation found in individuals with ASD was often greater than that for their typical peers. We identified the key regions of interest from our study above on typical adults that were indicative of social emotional processing. We then ran comparisons across those conditions between the participants with ASD and the typical controls. The resulting tests confirmed that there was greater activation in the social-emotional network in the brain for participants with ASD as shown in the bar graphs on Figure 5. However, there were no differences in other regions of general language processing that were engaged when listening to stories regardless of condition. The complete set of detailed results are in Appendix A.



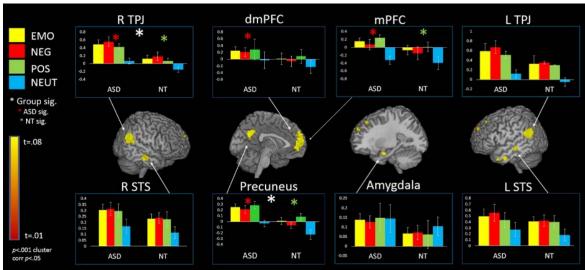


Figure 5. Regions of interest (ROI) from Sand (2015). Bar graphs show percent signal change in neural response to emotion (EMO; yellow), negative (NEG; red), positive (POS; green) and neutral (NEUT; blue) for individual ROI (y-axis), separated by autism (ASD) and neurotypical (NT) groups (x-axis). Error bars show standard error. * p < .05

Figure 4. Within group comparisons, Study 2. (A) Contrast of emotion (A), neutral (B), negative (C) and positive (D) scenarios in autism (ASD; red), neurotypical (NT; green). Task-related activity is displayed using a cluster corrected threshold of p < .001.

Conclusions

With respect to our timeline and basic commitments, we are still on schedule and have completed or are well underway to completing the project on time in accordance with our SOW. We have completed our preliminary study on healthy adults which has validated the experimental protocol that was proposed. We have successfully recruited and completed data collection on roughly 50% of our target number of human subjects for the sample of ASD and neurotypical peers. We are stepping up our recruitment efforts in order to meet our targeted goal of 60 participants. At this point without a complete set of data, we are remiss to make strong conclusions as to our primary hypotheses.

What opportunities for training and professional development has the project provided?

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

One of the largest benefactors from this project has been the training opportunities for graduate and undergraduate students that have had the opportunity to work directly on this investigation. As stated several places previously in this document, the preliminary analyses conducted for this project served as the basis for the doctoral dissertation of Dr. Lesley Sand who was the graduate student researcher funded on the grant in Year 1 and she has continued to serve as a post-doctoral researcher on the project through Years 2 and 3. Dr. Sand has worked closely over the course of this project with Drs. Bolger and Redcay in the preparation, data collection and data analysis as well as the manuscript and thesis writing involved for disseminating our findings. Dr. Sand has also attended a number of training workshops on special analysis techniques of MRI data using both Statistical Parametric Mapping (SPM) software as well as FreeSurfer, created by Harvard/Massachusetts General Hospital.

In addition to Dr. Sand, this grant has provided training opportunities for another doctoral student, Ms. Brandee Feola who is gaining valuable experience in working with patient populations with ASD to supplement her graduate training. Also, several undergraduates in the lab have contributed to this project enabling them to learn about brain imaging and analysis of MRI datasets. These undergraduate students have received direct mentoring from Dr. Sand as well as Dr. Bolger meeting weekly with both researchers. One of those students, Ms. Laura Casey, is now attending a Masters Degree program in Cognitive Neuroscience at the University of Glasgow in Scotland. Two students, Solana Lazarte and Connor Laughland are still working on the project in the lab.

How were the results disseminated to communities of interest?

The doctoral dissertation copyrighted by Dr. Sand and the University of Maryland (attached as Appendix A):

Sand, L. A. (2015). Neural Bases of Emotional Language Processing in Individuals with and without Autism. *Unpublished Doctoral Dissertation*, University of Maryland College Park. http://drum.lib.umd.edu/bitstream/handle/1903/17242/Sand_umd_0117E_16641.pdf?sequence=1

Manuscript submitted on Neurotypical adults to NeuroImage: Sand, L.A., Redcay, E., Zeffiro, T. and Bolger, D.J. (manuscript submitted for publication). Neural Bases of Emotional Language Processing.

Presentations to the International Meeting for Autism Research (IMFAR):

Sand, L.A., Redcay, E., Zeffiro, T., Samson, F. & Bolger, D.J. (2016) Hemispheric Differences in Auditory Complexity Processing in ASD. Presented at the International Meeting for Autism Research, Baltimore, MD: International Society for Autism Research.

Sand, L.A., Redcay, E., Zeffiro, T., & Bolger, D.J. (2016) Emotional Language Processing in Individuals with and without Autism Spectrum Disorder. Presented at the International Meeting for Autism Research, Baltimore, MD: International Society for Autism Research.

What do you plan to do during the next reporting period to accomplish the goals?

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Data Collection. During the next reporting period, we plan to continue data collection toward our goal of 30 reliable participants in each group (total of 60) with the expectation that some attrition will continue to occur. We expect to complete data collection between months 24-30 of the project.

Data Analysis. We will continue to analyze the current dataset with particular attention to the resting state functional connectivity (rs-fMRI) data that participants have contributed thus far. This data will enable us to examine the general connectivity of brain structures in our population of participants with ASD compared to our control sample with special interest in the regions engaged by our EIT paradigm.

Data Presentation. We will also prepare to present our the full set of FINAL data at Scientific Meetings and Conferences such as the International Meeting for Autism Research (IMFAR) in May of 2017.

4. IMPACT:

This component is used to describe ways in which the work, findings, and specific products of the project have had an impact during this reporting period. Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report. At this point of the project it is too early to have significant impact.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Actual or anticipated problems or delays and actions or plans to resolve them

There are no problems to report at this time. The project is actually ahead of schedule.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Dr. Sand is now serving a postdoctoral researcher on the project and will continue to through Years 2 and 3. We have hired a graduate student research assistant as of August 2016, Ms. Brandee Feola, to help with recruitment.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

The only modification to the human subjects protocol were an addendum to the informed consent procedure that would allow the data to be shared in a data repository, the ABIDE database, for MRI of patients with Autism Spectrum Disorder.

The ABIDE dataset is a database of structural MRI and resting-state functional MRI scans as well as behavioral measures collected from children and adults with autism spectrum disorders and typically developing controls that multiple sites across the US (and some international) contribute data to. The goal is for researchers to be able to aggregate across sites with a sample much larger than is possible with just one study. This large sample greatly enhances the reliability of the conclusions drawn and thus can have a greater impact on our understanding of autism spectrum disorders.

This change does not add any risks to participants. Those participants who contributed full datasets (that is, structural and resting-state functional MRI as well as behavioral data) (n=30) will be informed of this new addition to the consent form and asked if they are willing to have their de-identified data contributed, which they will indicate by electronic signature on the revised consent form.

This change has no impact on the scientific integrity of the study. The amendment was approved by local IRB on October 5, 2015 and submitted to HRPO who approved the amendment on December 5, 2015.

- **6. PRODUCTS:** List any products resulting from the project during the reporting period. Examples of products include:
- Publications, conference papers, and presentations

Sand, L.A., Redcay, E., Zeffiro, T., Samson, F. & Bolger, D.J. (2016) Hemispheric Differences in Auditory Complexity Processing in ASD. Presented at the International Meeting for Autism Research, Baltimore, MD: International Society for Autism Research.

Sand, L.A., Redcay, E., Zeffiro, T., & Bolger, D.J. (2016) Emotional Language Processing in Individuals with and without Autism Spectrum Disorder. Presented at the International Meeting for Autism Research, Baltimore, MD: International Society for Autism Research.

- Books or other non-periodical, one-time publications.
- Other publications, conference papers, and presentations

Sand, L. A. (2015). Neural Bases of Emotional Language Processing in Individuals with and without Autism. Unpublished Doctoral Dissertation, University of Maryland College Park. http://drum.lib.umd.edu/bitstream/handle/1903/17242/Sand_umd_0117E_16641.pdf?sequence=1

• Website(s) or other Internet site(s)

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

The Autism Brain Imaging Data Exchange (ABIDE): http://fcon_1000.projects.nitrc.org/indi/abide/

The ABIDE dataset is a database of structural MRI and resting-state functional MRI scans as well as behavioral measures collected from children and adults with autism spectrum disorders and typically developing controls that multiple sites across the US (and some international) contribute data to. The goal is for researchers to be able to aggregate across sites with a sample much larger than is possible with just one study. This large sample greatly enhances the reliability of the conclusions drawn and thus can have a greater impact on our understanding of autism spectrum disorders.

Other Products

5. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Donald J. Bolger
Project Role: Principal Investigator
Researcher Identifier (ORCID ID): 0000-0001-5114-8484
Nearest person month worked: 0.85 Academic, 3.0 summer

Contribution to Project: Dr. Bolger oversaw the execution of the research

protocol and monitored both recruitment and research

protocols.

Name: Elizabeth Redcay
Project Role: Co-Investigator

Researcher Identifier (ORCID ID): 0000-0002-1568-3102 Nearest person month worked: 0.85 Academic, 1.0 summer

Contribution to Project: Dr. Redcay was active in the planning of the project and

has provided support to Dr. Sand in the running of

participants.

Name: Lesley Sand

Project Role: Postdoctoral Researcher Researcher Identifier (ORCID ID): 0000-0002-0893-4081 Nearest person month worked: 9.0 Academic, 3.0 summer

Contribution to Project: Dr. Sand was largely responsible for recruitment of

participants and execution of the research protocol.

Name: Brandee Feola

Project Role: Graduate Student Research Assistant

Researcher Identifier (ORCID ID): N/A

Nearest person month worked: 9.0 Academic, 3.0 summer

Contribution to Project: Ms. Feola will aid in recruitment of participants and

execution of the research protocol.

Name: Tom Zeffiro Project Role: Consultant

Researcher Identifier (ORCID ID): 0000-0002-0893-4081 Nearest person month worked: 0.25 Calender (unpaid)

Contribution to Project: Dr. Zeffiro has been an unpaid consultant who has

provided previous training to Dr. Sand on functional brain imaging analysis and continues to advise on data

analysis and imaging protocols.

Name: Solana Lazarte

Project Role: Undergraduate Researcher

Researcher Identifier (ORCID ID):

Nearest person month worked: 0.25 Calender (unpaid)

Contribution to Project: Ms. Lazarte worked alongside Dr. Sand as an

undergraduate research to help analyze MRI data.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There is no change in overall effort by the PIs. Dr. Redcay's R01 proposal was funded in 2015 (details below). However, there is no overlap in effort or project goals.

NICHD R01

Hippocampal-memory network development and episodic memory in early childhood Role: co-I; time committed 1.35 academic months/year for 5 years

Direct costs: \$1,835,112

Overlap: None

Project Description: These studies will examine structural and functional development of hippocampal-memory network in early childhood and its relation to episodic memory abilities.

What other organizations were involved as partners?

Nothing to Report

6. SPECIAL REPORTING REQUIREMENTS: None

7.	APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.		